Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371:424-33. DOI: 10.1056/NEJMoa1405095

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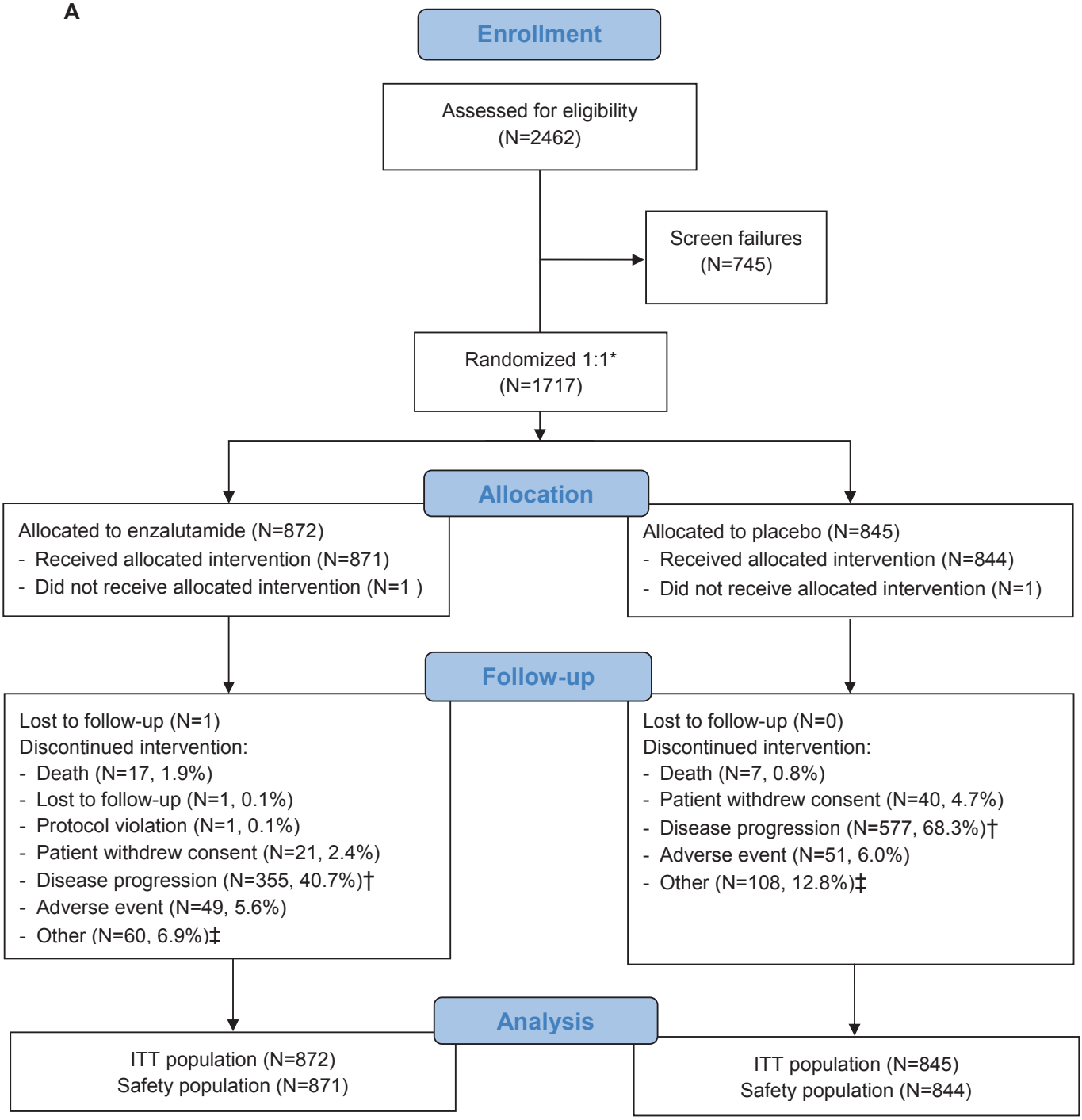
Figure S1. CONSORT Diagram.

A



* Randomization was stratified by study site.

† See Panel B for additional details.

‡ Majority discontinued due to rising PSA.

ITT denotes intent-to-treat.

B

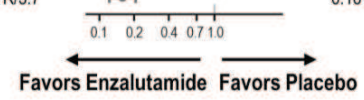
Discontinuation of Study Drug Due to Disease Progression.

Reason for Treatment Discontinuation	Enzalutamide (n=872)	Placebo (n=845)	Total (N=1717)
Disease progression – no. (%)	355 (40.7)	577 (68.3)	932 (54.3)
Radiographic progression*	285 (32.7)	461 (54.6)	746 (43.4)
Clinical progression*	85 (9.7)	150 (17.8)	235 (13.7)
Skeletal-related event*	44 (5.0)	46 (5.4)	90 (5.2)

* Patients can be summarized for more than one category but can only be counted once for each category.

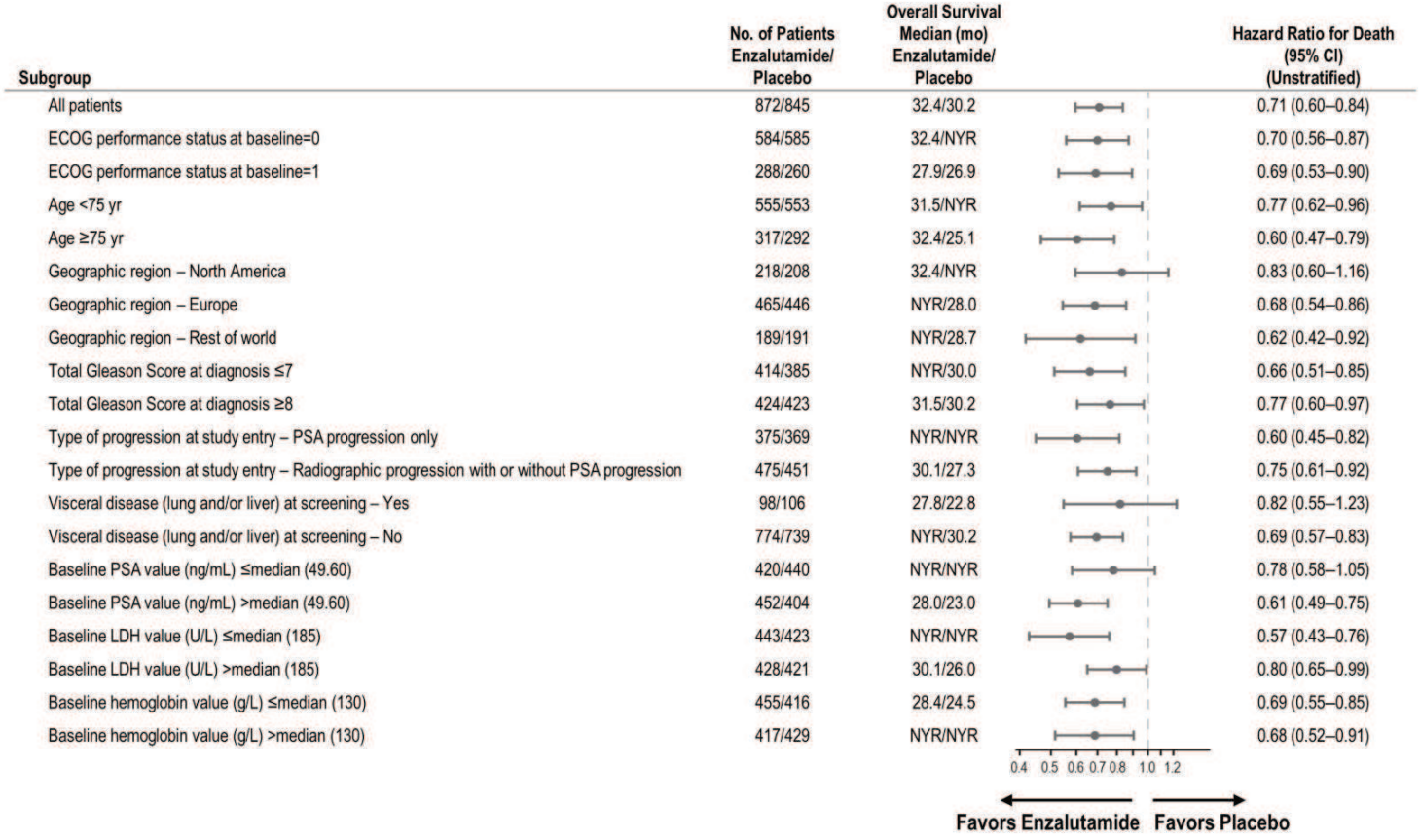
Figure S2. Subgroup Analyses for Radiographic Progression-Free Survival.

Subgroup	No. of Patients Enzalutamide/ Placebo	rPFS Median (mo) Enzalutamide/ Placebo	Hazard Ratio for rPFS (95% CI) (Unstratified)
All patients	832/801	NYR/3.9	0.19 (0.15–0.23)
ECOG performance status at baseline=0	557/549	NYR/3.7	0.15 (0.11–0.20)
ECOG performance status at baseline=1	275/252	14.1/4.0	0.27 (0.19–0.37)
Age <75 yr	529/517	NYR/4.6	0.20 (0.15–0.26)
Age ≥75 yr	303/284	NYR/3.7	0.17 (0.12–0.24)
Geographic region – North America	214/204	NYR/4.8	0.17 (0.12–0.25)
Geographic region – Europe	456/435	13.8/3.8	0.21 (0.15–0.28)
Geographic region – Rest of world	162/162	NYR/3.7	0.14 (0.08–0.25)
Total Gleason Score at diagnosis ≤7	401/370	14.1/5.3	0.16 (0.11–0.22)
Total Gleason Score at diagnosis ≥8	399/394	NYR/3.7	0.23 (0.17–0.31)
Type of progression at study entry – PSA progression only	348/341	NYR/5.6	0.16 (0.11–0.24)
Type of progression at study entry – Radiographic progression with or without PSA progression	464/435	14.1/3.7	0.18 (0.14–0.24)
Visceral disease (lung and/or liver) at screening – Yes	97/101	NYR/3.6	0.28 (0.16–0.49)
Visceral disease (lung and/or liver) at screening – No	735/700	14.1/4.0	0.17 (0.14–0.22)
Baseline PSA value (ng/mL) ≤median (51.10)	395/411	NYR/5.5	0.16 (0.11–0.23)
Baseline PSA value (ng/mL) >median (51.10)	437/389	13.8/3.6	0.18 (0.14–0.24)
Baseline LDH value (U/L) ≤median (185)	427/402	14.1/4.0	0.14 (0.10–0.20)
Baseline LDH value (U/L) >median (185)	404/398	NYR/3.8	0.23 (0.17–0.31)
Baseline hemoglobin value (g/L) ≤median (130)	429/388	14.1/3.7	0.24 (0.18–0.31)
Baseline hemoglobin value (g/L) >median (130)	403/413	NYR/5.3	0.13 (0.09–0.19)
Baseline bisphosphonate or denosumab use – Yes	215/222	13.8/5.6	0.27 (0.18–0.41)
Baseline bisphosphonate or denosumab use – No	617/579	NYR/3.7	0.16 (0.12–0.21)



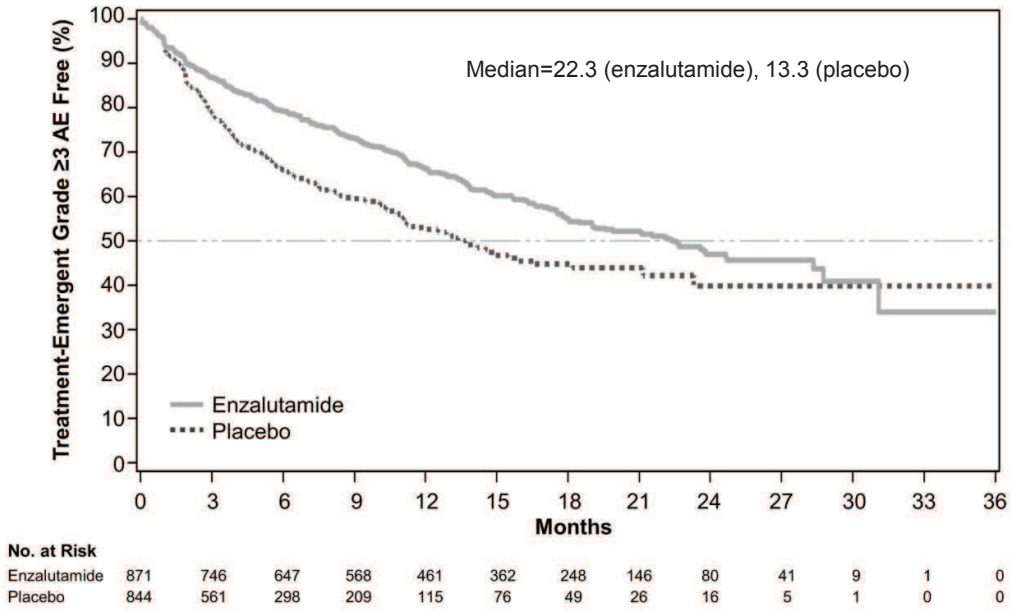
CI denotes confidence interval, ECOG Eastern Cooperative Oncology Group, LDH lactate dehydrogenase, NYR not yet reached, PSA prostate-specific antigen, rPFS radiographic progression-free survival.

Figure S3. Subgroup Analyses for Overall Survival.



CI denotes confidence interval, ECOG Eastern Cooperative Oncology Group, LDH lactate dehydrogenase, NYR not yet reached, PSA prostate-specific antigen.

Figure S4. Time to Grade 3 or Higher Adverse Event.



AE denotes adverse event.

Table S1. Definition of Study End Points.

End Point Variable	Definition and Analysis Method
Radiographic progression-free survival*	Radiographic progression-free survival, the coprimary end point, was defined as the time from randomization to the first objective evidence of radiographic disease progression assessed by the blinded independent central review facility or death due to any cause within 168 days after treatment discontinuation, whichever occurred first. Radiographic disease progression included confirmed bone disease progression and soft tissue disease progression. Radiographic disease progression was evaluated by independent central radiology review using the PCWG2 guidelines for bone disease and RECIST 1.1 for soft tissue disease. Radiographic disease progression in bone (2 or more new lesions on radionuclide bone scan) observed at week 9 required 2 additional new lesions on a confirmatory scan at least 6 weeks later; radiographic disease progression in bone observed after week 9 required persistence of 2 new lesions on a confirmatory scan at least 6 weeks later. Radiographic disease progression in soft tissue did not require a confirmatory scan for purposes of analysis. Patients who had no baseline or no postbaseline tumor assessments were censored on the date of randomization. Patients who had not progressed or died by the data cutoff date were censored on the date of the last radiographic assessment showing no evidence of disease progression prior to the data cutoff date. Continued radiographic imaging was not required after radiographic progression was confirmed. A 2-sided, unstratified log-rank test was used to compare radiographic progression-free survival between the treatment groups (enzalutamide and placebo).
Overall survival*	Overall survival, the coprimary end point, was defined as the time from randomization to death from any cause for each patient. A 2-sided (unstratified) log-rank test was used to compare overall survival between the treatment groups (enzalutamide and placebo).
Time to initiation of cytotoxic chemotherapy†	The time to initiation of cytotoxic chemotherapy was defined as the time from randomization to initiation of a cytotoxic chemotherapy. Cytotoxic chemotherapy was defined as the use of any of the following antineoplastic agents for prostate cancer: docetaxel, cabazitaxel, mitoxantrone, estramustine, cisplatin, carboplatin, cyclophosphamide, doxorubicin, mitomycin, irinotecan, 5-fluorouracil, gemcitabine, or etoposide. An unstratified log-rank test was used to compare treatment groups.
Time to first skeletal-related event†	The time to first skeletal-related event was defined as the time from randomization to the first occurrence of a skeletal-related event. A skeletal-related event was defined as radiation therapy or surgery to bone for prostate cancer, pathological bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. An unstratified log-rank test was used to compare the treatment

	groups.
Best overall soft tissue response†	The best overall soft tissue response was assessed using RECIST 1.1 and was defined as patients with a best overall soft tissue response consistent with a partial response or a complete response. Only patients with measurable soft tissue disease at baseline (defined as having at least 1 target lesion on CT or MRI scans according to RECIST 1.1) were included in the analysis.
Time to PSA progression†	For patients with PSA declines at week 13, the PSA progression date was defined as the date that a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir was documented. This increase was confirmed by a second consecutive value obtained at least 3 weeks later. For patients without PSA decline at week 13, the PSA progression date was defined as the date that a ≥25% increase and an absolute increase of ≥2 ng/mL above baseline was documented, which was confirmed by a second consecutive value at least 3 weeks later. Time to PSA progression was defined as the time from randomization to first confirmed PSA progression for all patients. An unstratified log-rank test was used to compare treatment groups.
PSA response†‡	Confirmed PSA responses, defined as ≥50%† and ≥90%‡ reductions in PSA from baseline to the lowest post-baseline PSA result as determined by the local laboratory, were calculated by treatment group for patients with PSA values at the baseline assessment and at least 1 postbaseline assessment. A consecutive assessment conducted at least 3 weeks later was required to confirm the PSA response. An unstratified Cochran-Mantel-Haenszel score test was used to compare the response rates between the enzalutamide-treated and placebo groups.
Functional Assessment of Cancer Therapy–Prostate (FACT-P)‡	The FACT-P is a multidimensional, self- reported quality-of-life instrument used with prostate cancer patients, consisting of 27 core items to assess patient function in 4 domains—physical, social/family, emotional, and functional well-being—and is supplemented by 12 specific items to assess disease-related symptoms. Each item is rated on a 0 to 4 Likert-type scale and then combined to produce subscale scores for each domain, as well as a global quality-of-life score. Higher scores represent better quality of life. The time to degradation of the FACT-P global score was defined as time from randomization to first assessment with at least a 10-point decrease from baseline in the total FACT-P score. An unstratified log-rank test was used to compare treatment groups.

PCWG2 denotes Prostate Cancer Clinical Trials Working Group, PSA prostate-specific antigen, RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1.

∗ Coprimary end point.

† Secondary end point.

‡ Prespecified exploratory end point.

Table S2. Demographic and Baseline Patient Characteristics (ITT Population).

Baseline Characteristic	Enzalutamide (N=872)	Placebo (N=845)
Age		
Median	72.0	71.0
Range	43.0–93.0	42.0–93.0
Age category – years, no. (%)		
<65	179 (20.5)	179 (21.2)
65 to 74	376 (43.1)	374 (44.3)
≥75 to 84	274 (31.4)	240 (28.4)
≥85	43 (4.9)	52 (6.2)
Race – no. (%)		
American Indian or Alaska Native	1 (0.1)	0
Asian	85 (9.7)	82 (9.7)
Black or African American	21 (2.4)	13 (1.5)
Native Hawaiian or other Pacific Islander	1 (0.1)	1 (0.1)
White	669 (76.7)	655 (77.5)
Other, multiple, unknown	95 (10.9)	94 (11.1)
Ethnicity – no. (%)		
Not Hispanic or Latino	784 (89.9)	743 (87.9)
Hispanic or Latino	16 (1.8)	22 (2.6)
Not reported, unknown	72 (8.3)	80 (9.5)
Baseline weight – kg		
No.	870	844
Median	83.1	82.8
Range	48.9–162.2	33.9–160.2
Body mass index – kg/m^2		
No.	870	843
Median	27.5	27.5
Range	17.5–46.8	15.3–50.6
Baseline ECOG performance status – no. (%)		
0	584 (67.0)	585 (69.2)
1	288 (33.0)	260 (30.8)
≥2	0	0
Baseline mean pain score – BPI-SF question 3		
No.	859	840
0 to 1 – no. (%)	569 (66.2)	567 (67.5)
2 to 3 – no. (%)	275 (32.0)	262 (31.2)
>3 – no. (%)	15 (1.7)	11 (1.3)
Baseline hemoglobin – g/L		
Median	130.0	131.0
Range	82.0–168.0	74.0–167.0
Baseline alkaline phosphatase – U/L		
Median	94.0	86.0
Range	34.0–4485.0	27.0–2350.0

Baseline Characteristic	Enzalutamide (N=872)	Placebo (N=845)
Baseline lactate dehydrogenase – U/L		
No.	871	844
Median	185.0	185.0
Range	52.0–1861.0	67.0–2321.0
Baseline serum albumin – g/L		
Median	38.0	39.0
Range	25.0–48.0	28.0–49.0
Baseline serum PSA – µg/L		
No.	872	844
Median	54.1	44.2
Range	0.1–3182.0	0.3–3637.0
Baseline creatinine – µmol/L		
Median	85.0	87.0
Range	29.0–207.0	41.0–218.0
Baseline use of corticosteroids >7 days∗ – no. (%)	35 (4.0)	36 (4.3)
History of cardiovascular disease† – no. (%)	179 (20.5)	168 (19.9)

Eligibility based on screening values.

∗ Includes all steroid use for prostate cancer on the date of first dose of study drug and with continuous exposure for at least 7 days.

† History of prior cardiovascular disease is based on medical history.

BPI-SF denotes Brief Pain Inventory Short Form, ECOG Eastern Cooperative Oncology Group, ITT intent-to-treat, PSA prostate-specific antigen.

Table S3. Baseline Disease Characteristics (ITT Population).

Baseline Disease Characteristic	Enzalutamide (N=872)	Placebo (N=845)
Time (months) from initial diagnosis or first treatment of prostate cancer to randomization		
No.	872	844
Median	62.7	64.6
Range	0.2–326.6	0.1–275.4
Total Gleason score category		
No.	838	808
≤7 – no. (%)	414 (49.4)	385 (47.6)
≥8 – no. (%)	424 (50.6)	423 (52.4)
Type of disease progression at study entry – no. (%)		
PSA progression only	375 (43.0)	369 (43.7)
Radiographic progression with PSA	349 (40.0)	344 (40.7)
Radiographic progression without PSA	126 (14.4)	107 (12.7)
No disease progression per protocol	22 (2.5)	25 (3.0)
Disease localization at screening* – no. (%)		
Bone only	348 (39.9)	335 (39.6)
Soft tissue only	124 (14.2)	149 (17.6)
Both bone and soft tissue	393 (45.1)	355 (42.0)
None	7 (0.8)	6 (0.7)
Distribution of disease at screening – no. (%)		
Bone	741 (85.0)	690 (81.7)
Lymph node	437 (50.1)	434 (51.4)
Visceral disease (lung or liver)	98 (11.2)	106 (12.5)
Visceral liver	40 (4.6)	34 (4.0)
Visceral lung	64 (7.3)	75 (8.9)
Visceral lung and liver	6 (0.7)	3 (0.4)
Other soft tissue†	113 (13.0)	105 (12.4)
Use of prior antiandrogen therapies – no. (%)	760 (87.2)	730 (86.4)
Number of prior antiandrogen therapies – no. (%)		
0	112 (12.8)	115 (13.6)
1	573 (65.7)	561 (66.4)
2	165 (18.9)	151 (17.9)
≥3	22 (2.5)	18 (2.1)
Number of bone metastases at screening – no. (%)		
0	131 (15.0)	155 (18.3)
1 to 9	456 (52.2)	418 (49.5)
10 to 20	140 (16.1)	122 (14.4)
>20	145 (16.6)	150 (17.8)

* Disease localization is based on the target lesion, nontarget lesion, and bone scan case report forms.
† Other soft tissue includes pelvic mass, adrenal mass, etc.
ITT denotes intent-to-treat, PSA prostate-specific antigen.

Table S4. Updated Overall Survival Analysis*.

	Enzalutamide (N=872)	Placebo (N=845)
Median overall survival follow-up, months	26.2	26.5
Number of deaths (%) at time of analysis	299 (34)	357 (42)
Median duration of overall survival, months	NR	31.0
Hazard ratio (95% CI)	0.73 (0.63, 0.85)	
P value	<0.001	

NR=Not reached; CI=Confidence Interval

*Through data cutoff date of January 15, 2014.

Table S5. Postbaseline Antineoplastic Therapy Use (ITT Population).

Postbaseline Antineoplastic Therapy Use	Enzalutamide (N=872)	Placebo (N=845)
Patients taking any postbaseline antineoplastic therapy – no. (%)	382 (43.8)	642 (76.0)
Patients taking at least one of the following postbaseline antineoplastic therapies – no. (%)	351 (40.3)	594 (70.3)
Docetaxel	286 (32.8)	479 (56.7)
Abiraterone acetate	179 (20.5)	385 (45.6)
Cabazitaxel	51 (5.8)	110 (13.0)
Sipuleucel-T	12 (1.4)	10 (1.2)
Enzalutamide	9 (1.0)	37 (4.4)

ITT denotes intent-to-treat.

Table S6. Adverse Events of Fatigue by Grade.

	Enzalutamide (N=871)	Placebo (N=845)
Fatigue (all grades) – no. (%)	310 (35.6)	218 (25.8)
Grade 1	187 (21.5)	118 (14.0)
Grade 2	107 (12.3)	84 (10.0)
Grade 3	16 (1.8)	16 (1.9)
Grade 4	0 (0.0)	0 (0.0)
Grade 5	0 (0.0)	0 (0.0)